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Contingency learning deficits and generalization in chronic unilateral hand pain patients

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Abstract

Contingency learning, in particular the formation of danger beliefs, underpins conditioned fear and avoidance behavior, yet equally important is the formation of safety beliefs. That is, when threat beliefs and accompanying fear/avoidance spread to technically safe cues, it might cause disability. Indeed, such *overgeneralization* has been advanced as a transdiagnostic pathological marker, but it has not been investigated in chronic pain. Using a novel hand pain scenario contingency learning task, we tested the hypothesis that chronic hand pain patients demonstrate less differential pain expectancy judgments due to poor safety learning, and broader generalization gradients, than healthy controls. Participants viewed digitized 3-D hands in different postures presented in random order (conditioned stimulus, CSs) and rated the likelihood that a fictive patient would feel pain when moving the hand into that posture. Subsequently, the outcome (pain/no pain) was presented on the screen. One hand posture was followed by pain (CS+), another was not (CS-). Generalization was tested using novel hand postures (generalization stimuli, GSs) that varied in how similar they were to the original CSs. Patients, but not healthy controls, demonstrated a contingency learning deficit determined by impaired safety learning, but not by exaggerated pain expectancy towards the CS+. Patients showed flatter, asymmetric generalization gradients than the healthy controls did, with higher pain expectancy for novel postures that were more similar to the original CS-. The results clearly uphold our hypotheses and suggest that contingency learning deficits might be important in the development and maintenance of the chronic pain-related disability.

Perspective:

Chronic hand pain patients demonstrate 1) reduced differential contingency learning determined by a lack of safety belief formation, but not by exaggerated threat belief formation, 2) flatter, asymmetric generalization gradients than the healthy controls.

1. Introduction

Contingency learning is adaptive – the ability to identify cues in our environment that signal threat or negative outcomes promotes survival by initiating avoidance (and other defensive responses); the ability to identify cues that signal reward or positive outcomes promotes approach behavior. Basic contingency learning, and more specifically the formation of danger expectancy beliefs, is indeed known to play a causal role in shaping conditioned physiological responses[6] and avoidance behavior[24] (for overviews see[2, 25]). For example, during classical fear conditioning – in which a neutral conditioned stimulus (CS) after repeated pairing with an aversive unconditioned stimulus (US) begins to elicit fear, anomalies in expectancy learning have been proposed to induce sustained anxiety[5, 13, 28, 41] and may in turn augment pain in susceptible individuals[27, 36]. Meta-analysis of experimental fear conditioning studies[21], together with more recent empirical evidence[11, 14, 15, 17, 23], revealed that, for pathological anxiety, the failure to inhibit fear in the presence of safety cues is more characteristic than excessive fear to danger cues.

Stimulus generalization, in which individuals extrapolate knowledge from one situation to another without actually having to experience the new situation, is also highly adaptive. However, when threat beliefs, and the accompanying persistent fear and avoidance, spread to a wide range of novel, neutral or technically safe cues, generalization may become overprotective. This process is considered maladaptive and is implicated in pathological anxiety-related disability [20, 22].

Nowadays, it is widely accepted that the conditions for learning a causal relationship between two neutral events closely resemble those that foster Pavlovian conditioning (with an intrinsically significant US)[9, 37]. Based on the well-established tradition of human contingency learning [7], and the presumed involvement of contingency learning deficits in chronic pain [16],

we developed a contingency learning task based around a clinical hand pain scenario. By assessing pain expectancy judgments as an index of contingency learning, we were able to evaluate contingency learning and generalisation without relying on experimentally induced pain or aggravating the patients' clinical symptoms. We hypothesized that people with chronic hand pain would demonstrate 1) less differential pain expectancy judgments (i.e. contingency learning deficit) due to poor safety learning, and 2) broader generalization gradients (i.e. expecting pain to a wider range of novel stimuli), than healthy controls.

2. Methods

2.1. Participants

The study used a convenience sample of 48 subjects including two gender and age group-matched[1] diagnostic groups: 24 hand pain patients (14 females; mean ± SD (range) age = 48 ± 14 (19–71) years and 24 healthy controls (14 females; mean ± SD (range) age = 47 ± 14 (16–67). The most important inclusion criterion for the hand pain group (HP) was to have unilateral pain at some part of the hand for at least 3 months. Patients were diagnosed with unilateral and chronic hand pain by a certified hand therapist before being notified of the study. Prior to data collection, current pain and average pain over the last two days, were assessed using a 101-point numerical rating scale (NRS), from 0 "no pain at all" to 100 "the worst pain you can imagine". The inclusion criterion for the healthy control group (HC) was to not have any hand pain. Exclusion criteria for both groups were: other pain conditions, diagnosed dyslexia, cognitive impairments or any condition that might influence the ability to make judgments or give verbal ratings (i.e., stroke, brain injury, diagnosed mental health condition). Hand pain patients were recruited from hand therapy clinics in metropolitan Adelaide, South Australia, and healthy controls were recruited via flyers, social media and

[1] Note – we did not use absolute age-matched groups, but 5-year age ranges to match the healthy controls to the hand pain patient group. We do not think that the capacity to make verbal pain expectancy judgments would be significantly different within the proposed age ranges.

word of mouth, also from metropolitan Adelaide. All participants provided written informed consent and the experimental protocol was approved by the institutional Human Research Ethics Committee. After data collection, participants completed the Fear of Pain Questionnaire-III [26], the Pain Catastrophizing Scale[40], and the Quick Disabilities of the Arm, Shoulder and Hand Outcome Measure (Quick DASH)[1]. More detailed demographic and clinical characteristics of both groups can be found in Table 1.

2.2.Stimulus material

Cues or conditioned stimuli (CS+/-), distractor stimuli (D1-4) and generalization stimuli (GS1-6) were hand pictures created with Poser (Smith Micro Software, Productivity and Graphics Division, Watsonville, CA, USA), a 3D animation program (see Figure 1). Hand pictures were presented in four different angles (two medial and two lateral orientations) in order to facilitate motor imagery based on mental rotation of one's own hand [33]. All stimuli were presented on a computer monitor, on a white rectangle with a black background screen. The outcome (US) was the text "pain" or "no pain" presented on the computer screen. Stimulus presentation was controlled by a program that was created with Affect 4.0, a Windows-based experimental software package[38].

2.3.Procedure

The experimental session lasted approximately 40 minutes. Patients were tested at the hand therapy clinic. Healthy controls were tested either at the University of South Australia or in their own home with a portable set-up. Data were collected by one of four experimenters (AM, RGM, JBE, JKB) evenly spread across both patients and controls. In all cases, every effort was made to ensure a quiet, softly lit and comfortable data collection environment. Participants received written information concerning the computerized task. The experimenter started the computer program and standardized instructions appeared on the screen (see

Appendix A for verbatim instructions). When the participant read the instructions, the experimenter asked if there were any questions or uncertainties regarding the task. The experimenter answered any possible questions and the participant proceeded with the task. During the task, the experimenter was present in the test room, but out of view of the participant.

2.3.1. Hand pain scenario contingency learning task

We adapted the food allergy task[7], a widely-used scenario contingency learning task, to make it relevant for hand pain patients. During the task, participants were presented with a set of hand pictures and they responded to each picture by predicting whether a fictive hand pain patient would feel pain when (s)he moves the hand into the posture displayed in the picture. Upon every hand picture presentation, after 2 s, the question "*How much do you expect the patient to feel pain?"* and an 11-point NRS, from 0 "totally not" to 10 "very much", appeared on the screen (see Figure 2). Participants used the left and right arrows of the keyboard to move a red dot on the rating scale, and then clicked the computer mouse to confirm their pain expectancy judgment. After they made a judgment, the outcome "PAIN" or "NO PAIN" appeared in the middle of the screen for 1.5 s. Then, the background of the computer screen cleared for 1 s, the following hand picture was presented, and the procedure was repeated. The pain rating for each picture was the primary outcome variable on which contingency learning and generalization gradients were evaluated.

The experiment consisted of three experimental phases: an *acquisition* phase, a *generalization* phase and a *cross-lateral generalization* phase (see design in Table 2). The acquisition phase was divided into two acquisition blocks, each consisting of 16 trials (pictures), presented in a semi-randomized order with the restriction that no more than two consecutive trials could be of the same type. Each acquisition block comprised 4 CS+

presentations, 4 CS- presentations and 2 presentations of each of the 4 distractor stimuli. The CS+ trials were followed by the "pain" outcome, the CS- and the distractor trials were followed by the "no pain" outcome. Which hand picture served as the CS+ and the CS- was counterbalanced across participants, and half of the participants received acquisition training with left hand pictures whereas the other half received acquisition training with right hand pictures. During the acquisition phase, all CSs were presented twice in each orientation (Figure 1) and the distractor stimuli were presented once in each orientation. The generalization phase included 32 trials, presented in a semi-randomized order with the restriction that no more than two consecutive trials could be of the same type. This phase consisted of 4 CS+ presentations, 4 CS- presentations and 4 presentations of each of the 6 GSs. The CS+ trials were again followed by the "pain" outcome, but the CS- and the GS trials were always followed by the "no pain" outcome. During this phase, all CSs and GSs were presented once in each orientation and generalization (GS) stimuli were of the same laterality as the acquisition (CS) stimuli. The cross-generalization phase was identical to the previous phase, except that 1) none of the trial types were followed by the "pain" outcome, and 2) mirrored hand pictures were used as GSs (that is, hand pictures showing the opposite hand in postures identical to those used for the previous phases).

2.4.Data analysis overview

The data were analyzed using a series of repeated measures analyses of variance (RM ANOVAs) to examine the differences in pain expectancy judgments between the hand pain patients and the healthy controls. To test our first main hypothesis: *Do chronic hand pain patients show less differential pain expectancy judgments (i.e. contingency learning deficit) due to poor safety learning?,* we conducted a RM ANOVA with between factor Group (2 levels – Patient/Control), and within factors Stimulus Type (2 levels – CS+/CS-), and Block (2 levels – ACQ1-2). Because we had clear *a priori* hypotheses, follow-up between-group

(Patient vs. Control) and within-group (Patient and Control separately) planned comparisons were used to compare *differential pain expectancy judgments* (CS+ vs. CS-) at the end of acquisition (ACQ2). Further, we calculated a between-group (Patient vs. Control) planned contrast to evaluate safety learning and danger expectancy learning (CS+ and CS- separately) during the acquisition phase (ACQ1-2).

To test our second main hypothesis: *Do chronic hand pain patients show flatter generalization gradients of pain expectancy judgments?,* we used a RM ANOVA with between factor Group (2 levels – Patient/Control) and within factor Stimulus Type (8 levels – CS+/CS-/GS1-6). Again, because we had clear *a priori* hypotheses, within-group (Patient and Control separately) and between-group (Patient vs. Control) linear and quadratic trend analysis were used to further test the differences in generalization.

Furthermore, two exploratory hypotheses were evaluated with secondary analyses. One analysis tested whether pain expectancy judgments were affected by the congruence between their own painful hand and the hand picture used as the CS+ in the experimental task. In particular, we expected that *patients might show stronger differential pain expectancy judgments when the fictive patients' pain in the experimental task matched the side on which they themselves reported clinical pain*. This post-hoc analysis was possible because approximately half of the participants had left hand pain (n = 13), and the other half had right hand pain (n = 11) and the design was balanced so that the hand pain scenario contingency learning task either included left or right hand pictures as CSs during the acquisition training. Thus, half of the patients received congruent acquisition training and the other half received incongruent acquisition training (*congruent*: left hand pain, left hand picture as CS+ or right hand pain, right hand picture as CS+; *incongruent*: left hand pain, right hand picture as CS+ or right hand pain, left hand picture as CS+). We carried out a RM ANOVA with factors Congruence (2 levels – congruent/incongruent), Stimulus Type (2 levels – CS+/CS-) and,

Block (2 levels – ACQ1-2) on the data of the patient group alone (n = 24). Post-hoc Scheffé within-group (congruent and incongruent separately) comparisons were used to compare differential pain expectancy judgments (CS+ vs. CS-) at the end of acquisition (ACQ2). Another secondary analysis was run to test cross-lateral generalization (test with right hand pictures, if acquisition and generalization tests were carried out with left hand pictures, and vice versa). We expected that *hand pain patients might generalize their pain expectancy more to the opposite hand pictures than healthy controls.* We conducted a RM ANOVA with factors Group (2 levels – Patient/Control) and Stimulus Type (8 levels – CS+/CS-/GS1-6). Statistical analyses were run with Statistica 11 software (Tulsa, OK, USA).

3. Results

3.1.Acquisition

As can be seen in Figure 3, pain expectancies were higher for the CS+ pictures than for the CS- pictures (main effect of Stimulus Type $F(1,46) = 65.88$, $p < 0.001$), and as predicted, this difference became greater in the second acquisition block than in the first acquisition block (Stimulus Type x Block interaction, $F(1, 46) = 33.44$, $p < .0001$). Moreover, this difference in pain expectancy between both CSs was smaller in the patient group than in the healthy controls (Stimulus Type x Group interaction, $F(1, 46) = 10.65$, $p < .01$) and developed differently during acquisition for the patients, as compared to the healthy controls (Stimulus Type x Group x Block interaction, $F(1, 46) = 7.03$, $p < .05$).

Planned comparisons further confirmed that both the patients (within-group contrast: $F(1, 46) = 11.77$, $p < .01$) and the healthy controls (within-group contrast: $F(1, 46) = 64.76$, $p < .0001$) successfully acquired differential pain expectancy judgments, but that differential learning was more substantial in the healthy control group than it was in the hand pain patient group (between-group contrast: $F(1, 46) = 13.63$, $p < .001$). Interestingly, patients did not

have higher pain expectancy ratings for the CS+, $F(1, 46) = 1.17$, $p = .28$, than the healthy controls had, but they did show higher pain expectancy ratings for the CS-, $F(1, 46) = 5.73$, $p < .05$.

The differential (CS+ *vs.* CS-) pain expectancy judgments (see Figure 4) did not seem to develop differently from the first acquisition block to the second depending on whether there was (in)congruence between the clinical pain and the hand picture (CS+) used to predict the fictive patient's pain, (Stimulus Type x Congruence x Block interaction, $F(1, 22) = 1.38$, $p = .25$). Although the 3-way interaction was not significant, we further interrogated this exploratory hypothesis that patients might learn better to expect pain in response to the CS+, when this hand picture corresponds to their own painful hand side. Interestingly, post-hoc Sheffé comparisons confirmed that at the end of the acquisition phase, patients did show differential pain expectancy ratings when they were trained with congruent hand pictures, $F(1, 22) = 11.85$, $p < .001$, but they did not show differential pain expectancy ratings when they were trained with incongruent hand pictures, $F(1, 22) = 3.20$, $p = .29$.

3.2.Generalization

Overall patients did not give higher pain expectancy judgments for the novel hand pictures that varied in similarity between the original CS+ and CS- (GSs) than healthy controls (main effect of Group, $F < 1$), but pain expectancy judgments did vary across these novel hand pictures in both groups (main effect for Stimulus Type, $F(7, 322) = 42.52$, $p < .0001$). More importantly, pain expectancy judgments for these novel pictures varied in a manner that was different between patients and controls (Stimulus Type x Group interaction, $F(7, 322) = 2.67$, $p < .05$). That is, pictures that were more similar to the CS- elicited higher pain expectancy judgments in the patients than they did in the healthy controls (see Figure 5). Planned comparisons revealed that there was linear decrease in pain expectancy judgment with

decreasing GS similarity to the CS+ for the healthy controls ($F(1, 46) = 61.68$, $p < .0001$), as well as for the patients, ($F(1, 46) = 19.29$, $p < .0001$). Interestingly however, this gradient decreased less steeply for the patients than it did for the healthy controls ($F(1, 46) = 5.99$, $p < .05$). There was also a quadratic decrease in the pain expectancy judgment for the healthy controls ($F(1, 46) = 25.55$, $p < .0001$), and the patients ($F(1, 46) = 17.69$, $p < .001$), but this quadratic decrease was not different between groups, $F < 1$.

3.3.Cross-lateral generalization

Pain expectancy judgments in response to the mirrored GSs, that is, pictures of the opposite hand to that used during generalization, varied with higher pain expectancy judgments for novel hand pictures that were more similar to the original CS+ (main effect for Stimulus Type, $F(7, 322) = 36.03$, $p < .0001$). As can be seen in Figure 5, overall patients had higher pain expectancy ratings during cross-lateral generalization than did healthy controls (main effect for Group, $F(1, 46) = 4.12$, $p < .05$), irrespective of stimulus type (Stimulus Type x Group, $F < 1$).

4. Discussion

The findings clearly support our first hypothesis that chronic unilateral hand pain patients show a contingency learning deficit in comparison with pain-free age and gender-matched controls. We found that in a simple contingency learning task based around a clinical hand pain scenario, the patients acquired less differential pain expectancy judgments than the healthy controls. As expected, this pain expectancy bias did not relate to the CS+, that is, patients did not expect the pain outcome to occur more following the hand postures that were actually paired with the pain outcome, but they did expect the pain outcome more with the hand postures that were never paired with the pain outcome (CS-). The study also provided preliminary evidence for our secondary hypothesis: the contingency learning deficit seemed to

be attenuated when the *a priori* pain beliefs of the patient matched the prearranged experimental contingencies. That is, when the hand picture paired with the painful outcome corresponded to the patient's own painful hand, the likelihood of picking up the contingency appeared greater, than when pictured hands corresponded to the patient's non-painful hand. Critically, this was an exploratory analysis and our three-way interaction was not significant, which means the hypothesis should be *a priori* tested in a subsequent study before the result is endorsed.

Our second hypothesis, that patients show a flatter generalization gradient than healthy controls, was also supported. Particularly, patients showed higher pain expectancies to novel hand postures that were increasingly similar to the safe (CS-) posture. We also found support for our secondary hypothesis relating to the more exploratory cross-lateral generalization test –generalization gradients were similar in both groups, but patients reported higher pain expectancy for all the mirrored hand pictures.

Contemporary associative learning theory proposes that learning is based on the information value of predictive cues and that conditioned defensive responses such as fear and anxiety are based on expectancy about the occurrence of aversive events[24, 25]. Contingency learning deficits are assumed to be critically involved in chronic pain-related disability. There is preliminary evidence that contingency learning during fear conditioning is disturbed in fibromyalgia patients –when a visual cue was reinforced with a painful heat stimulus in 50% of the trials, fibromyalgia patients appeared less likely to identify the contingency (50%) than rheumatoid arthritis patients (86%), who were in turn less likely to identify the contingency than healthy controls were (100%)[16]. The authors concluded that the rate of unaware fibromyalgia patients is high because they have fear learning deficits, although their design does not allow conclusions about mechanisms –for example changes in the nociceptive processing system or in the fear response system. The results of the present study, in which

we ruled out this possible confound because we did not explicitly induce fear nor pain in our protocol, suggest that the deficit might be rooted at a more basic associative learning level. We further suggest that such basic learning deficit induces increasing generalized anxiety, which might in turn lead to enhanced pain in chronic pain populations. Although speculative, this suggestion is not outrageous and would provide a missing link between associative fear learning and up-regulation of the nociceptive/pain system.

The contingency learning deficit in the patients was expressed by increased pain expectancy in response to hand postures that were never paired with the pain outcome (CS-), but patients did not expect the pain outcome to occur more following the hand postures that were in fact paired with the pain outcome. These results strongly suggest a lack of safety learning in these patients. These findings corroborate results from other fields –again mostly stemming from fear conditioning experiments– for example the lack of safety learning in clinical anxiety disorders[17, 23] and in healthy individuals with anxiety proneness[3, 11].

Overgeneralization has been advanced as a transdiagnostic pathological marker in diverse psychological disorders, for example depression[19], posttraumatic stress[17] and, panic[22, 23], but so far it has not been investigated with regard to chronic pain. In this study, we demonstrated that chronic hand pain patients showed a flatter generalization gradient than healthy controls. In particular, patients expected the pain outcome more when viewing the novel hand postures that were increasingly similar to the safe (CS-) posture. This asymmetrical generalization gradient is in line with the lack of inhibition to the non-painful hand posture during acquisition. Patients did not learn the safety of the CS-, and therefore they also expect the painful outcome more with the novel stimuli that are similar to the original CS-. No such asymmetry between healthy controls and patients was observed for the CS+, which is also reflected the generalization gradient. That is, patients do not expect the painful outcome more with the novel stimuli resembling the original CS+.

Some interesting findings deserve further attention. First, it should be noted that the acquisition training itself can be interpreted as a type of generalization learning, since the CS+ consisted of the same hand position presented in four orientations. This procedure was applied to induce motor imagery based on mental rotation of the hand pictures[8, 12, 34, 39]. We reasoned that imagined hand movements would be more relevant and salient for the hand pain patients than neutral 2-D pictures. We predicted that using 3-D pictures would promote attention to the pictures and enhance contingency learning[35]. As a consequence, participants had to integrate this information and generalize the pain expectancy across the four orientations of each stimulus type. It may be possible that patients are slower in extracting this information and formulating clear propositions, but the absence of any group differences for the CS+ suggests against this possibility.

Second, cross-lateral generalization gradients were similar for both groups, but patients reported higher pain expectancy for all the mirrored hand pictures. This pattern of results may be due to lower pain expectancy judgments for the mirrored CS+ than for the original CS+ in the healthy controls but not in the hand pain patients, probably because cross-lateral generalization was tested under extinction. More tentatively, this might imply that patients generalize their pain expectancy beliefs more to the opposite hand because they are more uncertain about the safety of these novel but related stimuli, or because they simply have more firm expectancy beliefs that are resistant to extinction.

One important methodological strength is that our experimental task offers the possibility to tap into very basic associative learning mechanisms and can be easily adapted to test other pain populations. We contend that fundamental pain research would benefit from the development and implementation of flexible, easily applicable and ethically approved experimental procedures to identify possible contingency learning deficits in different pain populations without the need to actually administer painful/aversive stimuli.

Of course, this study also has some limitations. First, in contrast to the Jenewein study[16], we did not include any other chronic or acute pain condition as a specificity control, but rather used the broad criterion of 'hand pain of at least three months duration'. Future research with particular conditions might yield idiosyncratic group differences, as has been documented for example, for the presence of dysynchiria, a sensory processing disorder, between CRPS and chronic neuropathic hand pain[18]. Second, this study does not allow us to draw conclusions about the causal relationship of this contingency learning deficit in the development of chronic pain-related disability. Prospective studies or follow-up of patients after successful exposure treatment might shed more light on these dynamics. More specifically, are these learning deficits present before the onset of chronic pain (i.e. vulnerability factor), or do they disappear/diminish after successful treatment (i.e. epiphenomenon of chronic pain)? Relevant to this is the demonstrated benefit of repeated left/right judgments of pictured hands (i.e. motor imagery) for people with CRPS of the hand[4, 30, 32, 42] –perhaps this effect relates to exposure and re-differentiation of painful and non-painful hand postures. That the time taken to make such judgments relates strongly to the pain that would be predicted on undertaken the shown movement[31]), and improves in advance of symptomatic relief[29] seems to support this idea. Third, groups differ at least on two aspects: hand pain patients have 1) a history of hand pain, and 2) real-life pain during the experimental task. Alternatively, both aspects might have influenced the contingency judgments. Pain interferes with cognitive tasks via attentional disruption[10] and contingency learning can be viewed as such a task. Future research should examine whether contingency learning in healthy participants is equally impaired during experimental pain.

To conclude, we have shown that chronic hand pain patients demonstrate a pain expectancy bias that is characterized by a lack of safety learning, but not by exaggerated pain expectancy towards the CS+, as compared with the healthy controls. Furthermore, we showed

that these patients showed flatter, asymmetric generalization gradients than the healthy controls, with higher pain expectancy for novel stimuli that were more similar to the original CS-. We argued that contingency learning deficits and more importantly *overgeneralization* – as a transdiagnostic pathological marker– represent a promising and underinvestigated pathological factor that might be relevant for pain disorders. Deficits in selective threat appraisal might cause anomalies in fear conditioning and, therefore, the maintenance of the chronic pain-related disability.

5. Disclosures

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8. Figure captions

Figure 1. Hand pictures used as conditioned stimuli, distractors and generalization stimuli.

Figure 2. Flow chart of the experimental task.

Figure 3. Mean pain expectancy judgments for the CS+ and the CS- for the hand pain patient group (*n* = 24) and the healthy control group (*n* = 24) separately during both acquisition blocks (ACQ1-2). Vertical bars denote 95% confidence intervals.

Figure 4. Mean online pain expectancy judgments for the CS+ and the CS- for the hand pain patients (*n* = 24) separately for those being trained with hand pictures corresponding to their own painful hand side (congruent; *n* = 12) and those being trained with hand pictures not corresponding to their own painful hand side (incongruent; *n* = 12) during both acquisition blocks (ACQ1-2). Vertical bars denote 95% confidence intervals.

Figure 5. Mean online pain expectancy judgments for the CS+ , CS- and the six generalization stimuli (GS1-6) for the hand pain patient group (*n* = 24) and the healthy control group (*n* = 24) separately during both the generalization phase and the cross-lateral generalization phase. Vertical bars denote 95% confidence intervals.

Appendix A. *Verbatim instructions of the scenario contingency learning task.*

Dear participant,

In this experiment, your task is to predict whether a fictive hand pain patient will have pain when he moves his hand into a certain position. A series of pictures displaying hand positions will be presented on the computer screen. Upon every presentation of a hand position, you will be asked to answer the following question: "*How much do you expect the patient to feel pain*?". A rating scale will appear at the bottom of the screen on which you can indicate your prediction.

The rating scale goes from 0 to 10, labeled respectively, '0' = *I totally not expect the patient to feel pain*, and '10' = *I very much expect the patient to feel pain*. Use the left and right arrows to move the cursor on the rating scale, and use a left mouse click to confirm your prediction.

After you have made your prediction, we will let you know whether the patient did or did not feel pain, so that you can evaluate the accuracy of your prediction. Your predictions will be random in the beginning of the experiment, but do not worry, gradually you will learn which hand positions cause pain in this patient.

Do you have any questions? If yes, please ask the experimenter for more explanation. If no, press <ENTER> to start the experiment.

Table 1. *Demographic and clinical characteristics for the hand pain patient group* (n = 24) *and healthy control group* (n = 24) *separately.*

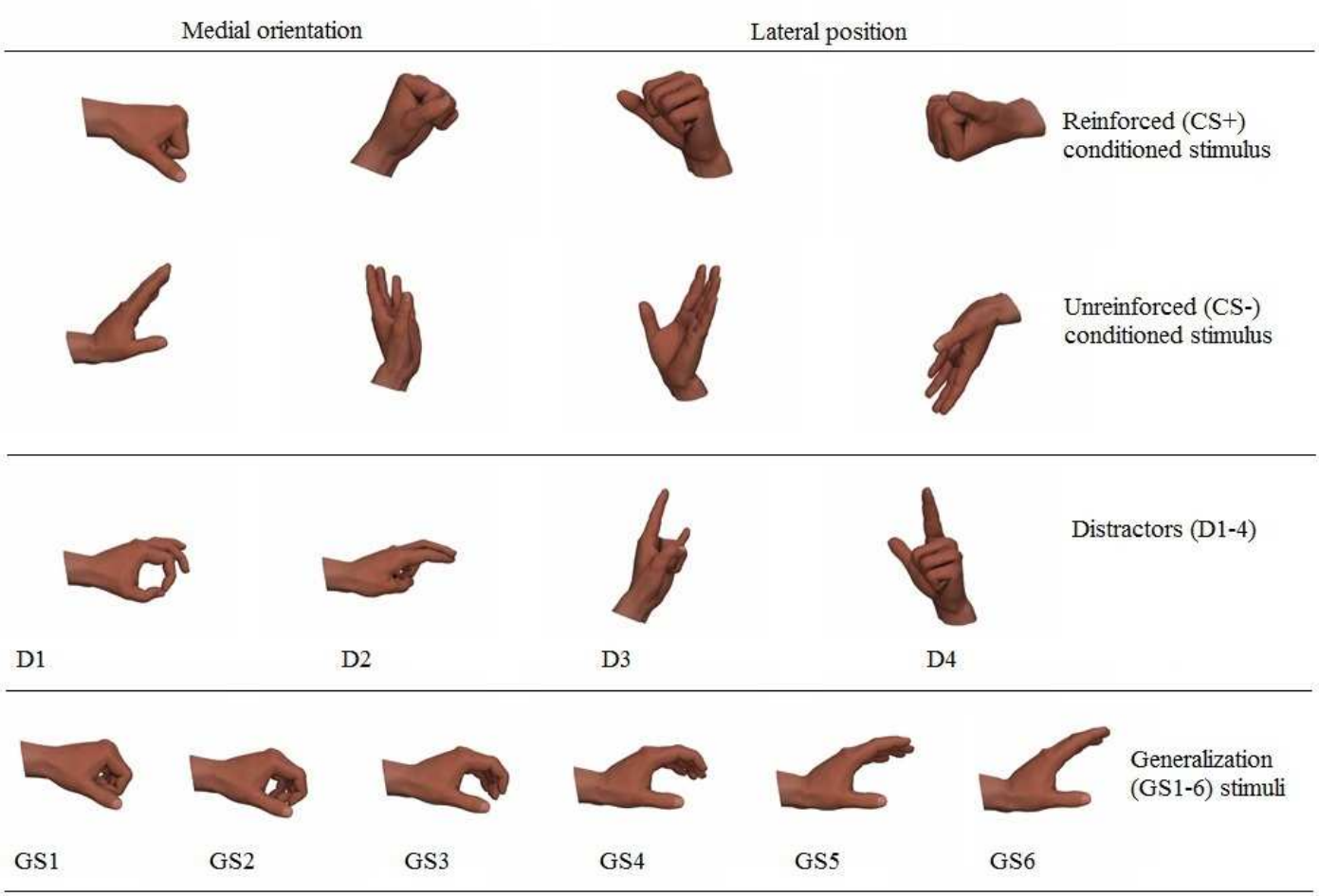
Total N = 48	Chronic Hand Pain Patient Group		Healthy Control Group	
	M (*SD*)	Range	*M* (*SD*)	Range
Age (in years)	48 (14)	19-71	47 (14)	16-67
Current Pain Report (0-100)	32.88 (23.35)	0-90		
Ongoing Pain Report (0-100)	38.44 (23.76)	0-80		
Duration of complaints (in months)	30.71 (62.98)	4-312		
Duration of therapy (in weeks)	58.25 (86.43)	1-364		
FPQ	83.96 (17.89)	52-108	77.88 (14.02)	53-108
FPQ – medical pain	24.92 (8.43)	11-39	25.33 (5.63)	17-37
FPQ – minor pain*	22.08 (6.17)	12-34	18.42 (4.62)	11-28
FPQ – severe pain	36.96 (6.59)	22-46	34.13 (7.99)	18-47
PCS	18.33 (7.60)	6-33	14.85 (10.00)	2-30
PCS – magnification	3.75 (1.48)	1-7	3.13 (2.17)	0-8
PCS – helplessness	8.08 (4.01)	2-16	5.90 (3.93)	0.5-12
PCS – rumination	6.50 (3.20)	1-14	5.83 (4.79)	0-15
QDASH – disability/symptom score (n = 23)	39.43 (20.58)	6.82-84.09		
QDASH – work (n = 18)	41.67 (30.47)	0-100		
QDASH – sport (n = 5)	58.75 (39.43)	0-100		

Note: FPQ = total score on the Fear Of Pain Questionnaire-III; PCS = total score on the Pain Catastrophizing Scale; QDASH = total score on the Quick DASH Outcome Measure. *M* = mean; *SD* = standard deviation; One patient failed to fill out the QDASH and was excluded from the statistical analysis. The optional modules of the QDASH can only be scored when patients are still employed or engaged in sports/cultural activities. *p < .05. The sample included 5patients (21%) with wrist pain, 6 (25%) with thumb pain, 2 (8%) with pain in another specific finger and, 11(46%) with more general hand pain; 13 of these patients had left hand pain and 11 patients had right hand pain. 7 patients (29%) used medication for pain relief.

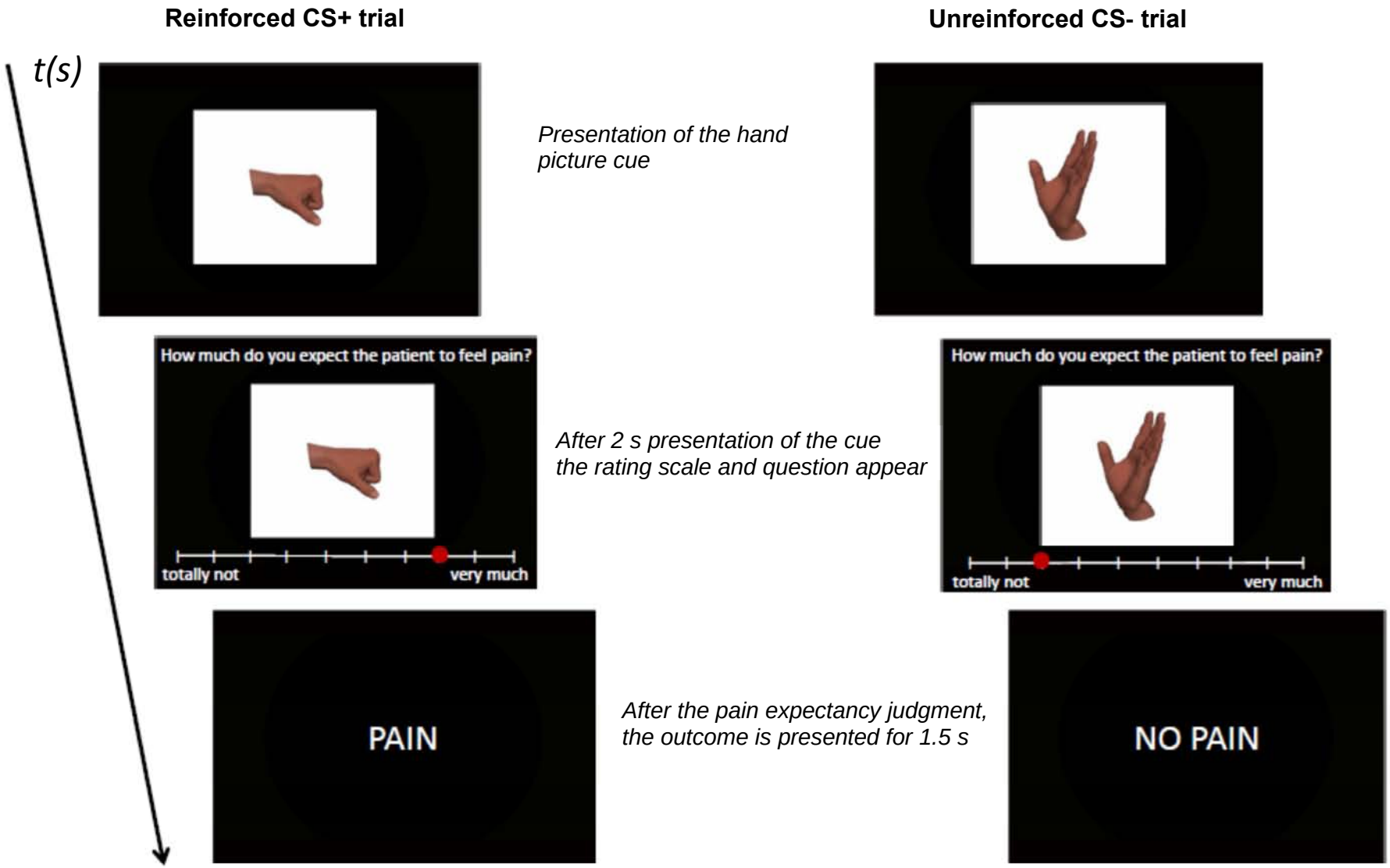
Table 2. *Experimental design.*

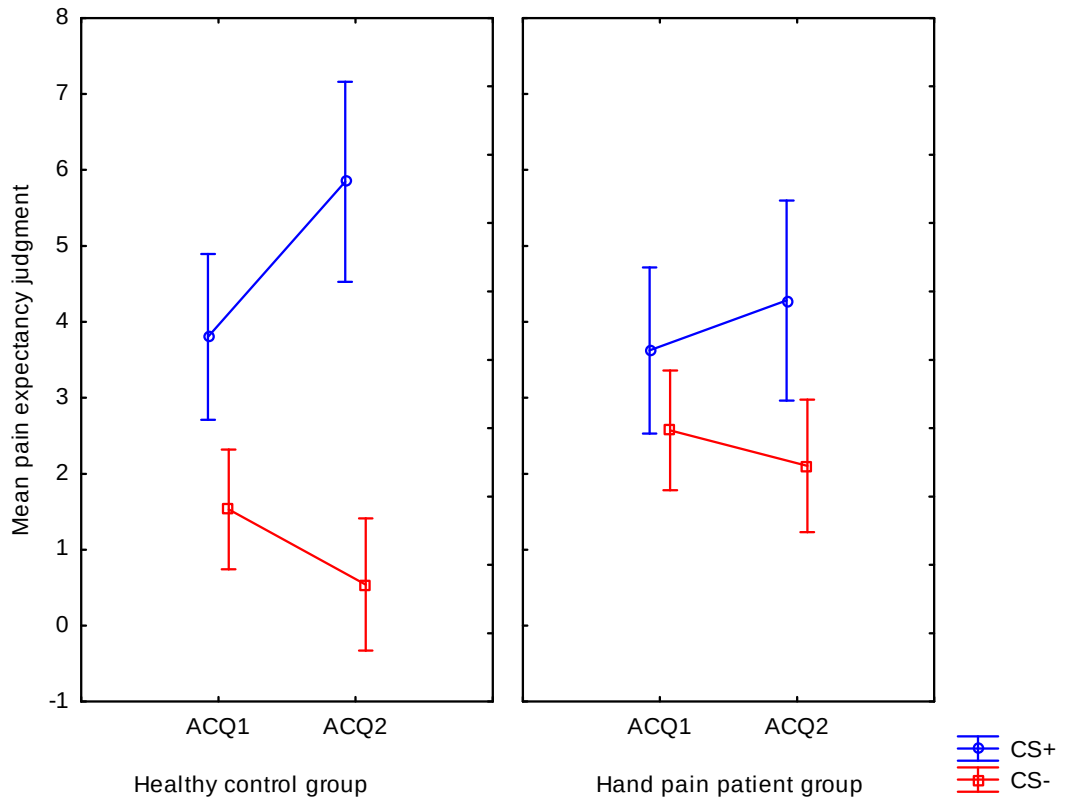
N = 48	ACQUISITION	GENERALIZATION	CROSS-LATERAL GENERALIZATION*
Hand pain patient group Healthy control group	8 x CS+ 8 x CS- 4 x D1-4	4 x CS+ 4 x CS- 4 x GS1-GS6	4 x mirror CS+ 4 x mirror CS- 4 x mirror GS1-GS6

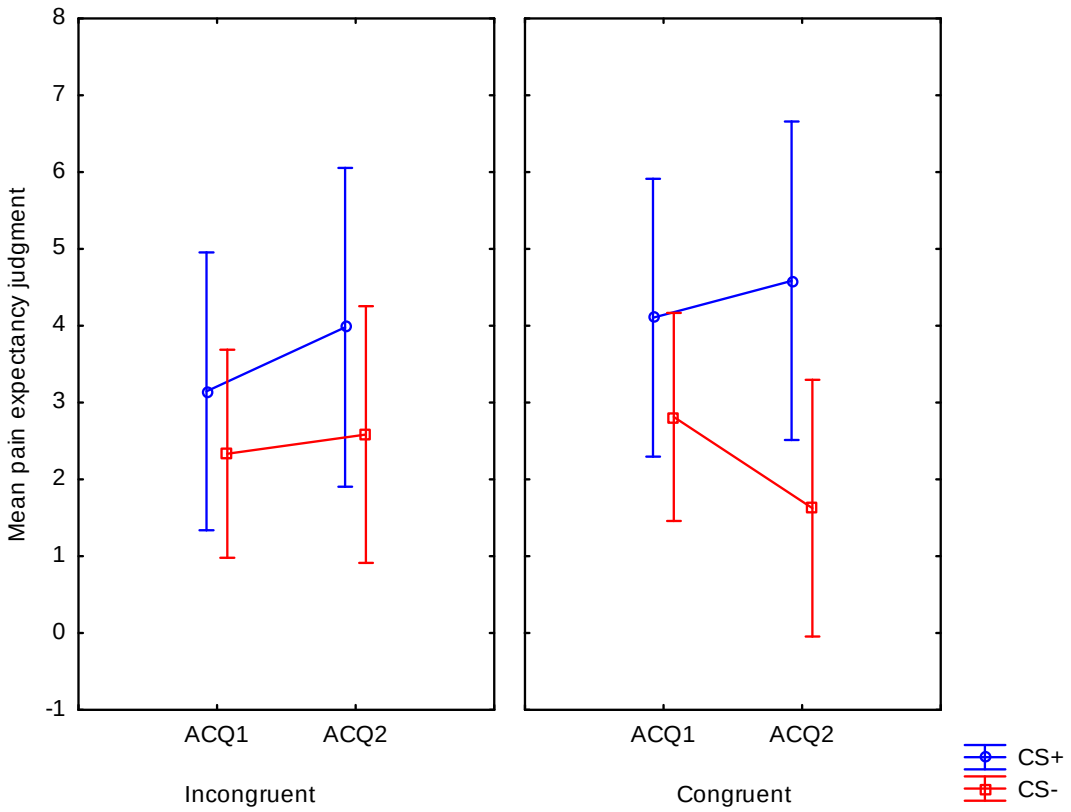
Note: CS+ and CS- are two hand positions (each presented in four orientations). CS+ and CS- pictures were counterbalanced across participants; D1-4 are distractors and GS1-GS6 are generalization stimuli. Stimuli are presented in a semi-randomized order with the restriction that no more than two consecutive pictures could be of the same stimulus type. *Mirror hand positions of the CS+ are not reinforced and GSs are never followed by the "pain outcome".

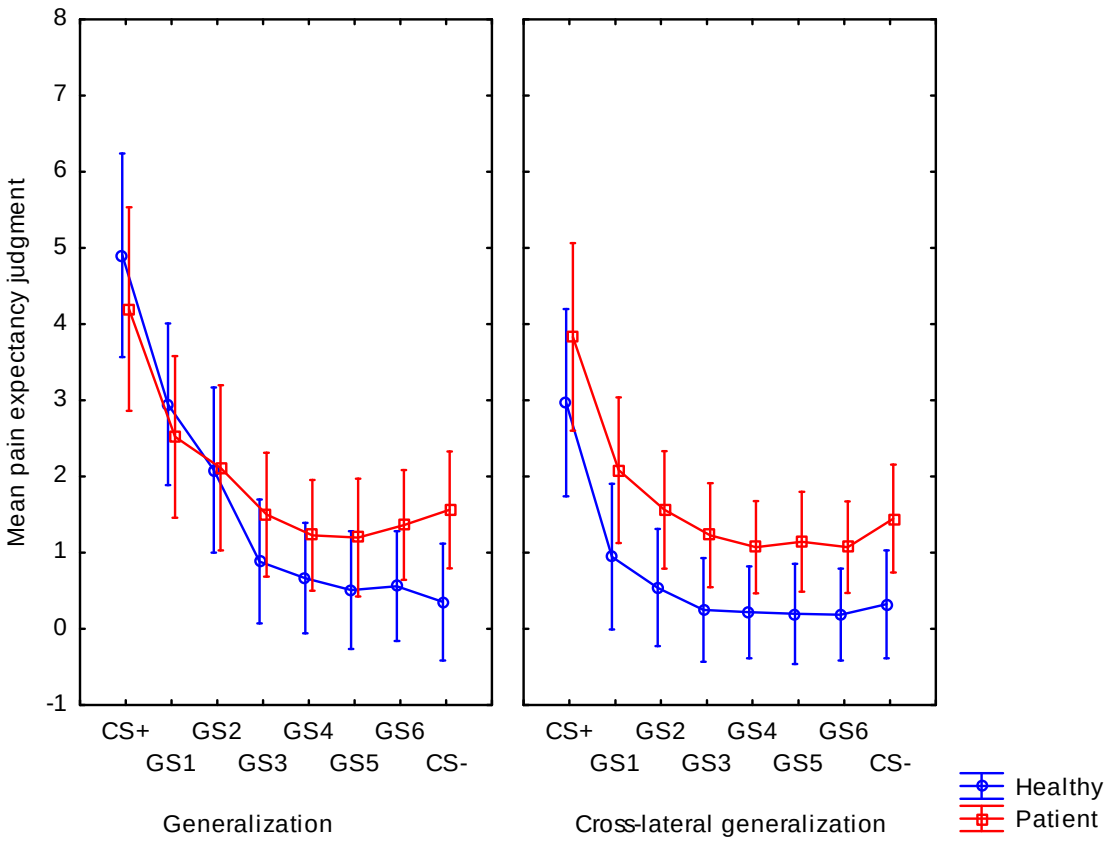


Note – Two hand pictures in 4 presentation angles (2 medial orientations and 2 lateral orientations) were used as the reinforced (CS+) and the unreinforced (CS-) conditioned stimulus (upper panel) and 4 hand pictures in 4 presentation angles served as distractor (D1-4) stimuli (middle panel); CS+ and CS- pictures were counterbalanced across participants. Six hand pictures of varying similarity with the CS+ to the CS- served as the generalization (GS1-6) stimuli.


Reinforced CS+ trial
Unreinforced CS- trial
t(s)
Presentation of the hand picture cue
How much do you expect the patient to feel pain?
totally not
very much
After 2 s presentation of the cue the rating scale and question appear
How much do you expect the patient to feel pain?
totally not
very much
PAIN
After the pain expectancy judgment, the outcome is presented for 1.5 s
NO PAIN







Highlights

Chronic hand pain patients demonstrate 1) reduced differential contingency learning determined by a lack of safety belief formation, but not by exaggerated threat belief formation, 2) flatter, asymmetric generalization gradients than the healthy controls.